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expressing said thymidine kinase gene to produce
Smooth muscle
thymidine kinase protein in, cells of said blood vessel; and
then administering to said mammal an effective amount of
a DNA replication-inhibiting nucleoside analog capable of
being phosphorylated by said thymidine kinase protein, whereby
said phosphorylated analog is preferentially incorporated into
the DNA of proliferating cells, and whereby said proliferating
cells are killed.

Remarks

Claim 2 has been canceled. Claim 1 has been amended.
Accordingly, Claims 1, 3-12 and 14-15 remain presented for
examination. The undersigned would like to thank Examiners Newell
and Stone for the courtesy extended to him and to Applicants during
the personal interview conducted on October 26, 1995. The
substance of that interview is accurately reflected in the
contemporaneous Examiner Interview Summary Record (Paper No. 10)
and is further incorporated into the foregoing amendment and these
remarks. Reconsideration and withdrawal of the present rejections
in view of the amendments and arguments presented herein are
respectfully requested.

Rejections under 35 U.S.C. §112

It is believed that the amendments presented herein were
favorably received during the interview. However, for the record,

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the reasons why the specification enables the present claims are discussed in detail below.

The PTO maintained that the pAd.HSV-tk vector should be deposited, asserting that it was unlikely that the skilled artisan would be able to obtain the precise vector disclosed by Applicants which could influence the expression level of the tk gene in transduced cells. It is not required that the skilled artisan be able to obtain the identical construct as that disclosed by Applicants, as long as a similar construct capable of directing HSV-tk expression can be synthesized from available starting materials using the specification and/or well known methods as guidance.

Further, there is no requirement for Applicants to deposit the "best" construct. The court has held that the failure to deposit an admittedly "best" monoclonal antibody did not violate § 112 because the process of obtaining such monoclonal antibodies was fully disclosed in the specification Scripps Clinic and Research Foundation v. Genentech, Inc. 18 USPQ 2d 1001, 1017. In other words, as long as Applicants enable production of similar vectors useful in practicing the invention, they need not deposit the particular vector used in the specification. In Hybritech, Inc. v. Monoclonal Antibodies, Inc. (231 USPQ 81, 95), the court stated that even though the details of monoclonal antibody production were not disclosed, the "existence of monoclonal antibodies having the affinity constant claimed in the patent was well known." Here, the

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production of similarly effective adenoviral vectors is well within the skill of the art as enabled by the present specification.

Therefore, the law clearly indicates that the deposit of adenoviral vector pAd.HSV-tk is not required to satisfy the enablement requirement.

The PTO maintained that the porcine model did not accurately reflect what would be expected to occur in humans. In their previous response, Applicants provided solid evidence that the porcine model of restenosis is the most art-accepted model of what would occur in humans and maintain that the PTO is erroneously raising an operability/utility issue by requiring human data to satisfy the enablement requirement. Enclosed herewith is a publication by Muller et al. (*J. Am. Coll. Cardiol.*, 19:418-432, 1992) which states that "of all the animal species systematically examined to date, the pig is the most similar to humans in its cardiovascular morphology and physiology and susceptibility to atherosclerosis. The coronary arteries of the adult pig approximate the size of human coronary arteries and have a very similar morphologic structure." (See p. 424).

Nonetheless, in the amended claims, the successful inhibition of restenosis in humans is not required. The claims are now directed to a method of inhibiting vascular cell proliferation, not to the therapeutic inhibition of restenosis. The PTO acknowledged at the interview that this amendment would be helpful in addressing

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the enablement rejection. The evidence of record clearly indicates that inhibiting vascular cell proliferation has been enabled.

The Office Action maintained that the specification did not present sufficient guidance to enable the skilled artisan to treat any and all mechanically treated blood vessels in any and all mammals, including humans, without undue experimentation. The specification as filed contains experimental data obtained from a porcine animal model of restenosis evidencing the success of the claimed method. (See Example 4). Further, the declaration of Dr. Elizabeth Nabel, enclosed herewith, presents additional experimental data demonstrating the efficacy of the claimed method in the inhibition of vascular cell proliferation in three species: rat, pig and rabbit. (Decl., ¶2). Additionally, an alkaline phosphatase gene contained within an adenoviral vector was expressed in both human blood vessels and atherosclerotic rabbit blood vessels (Decl., ¶2), demonstrating the ability of the vector to traverse fatty atherosclerotic deposits and enter the cells of the vessel wall.

These experiments were performed using the same parameters as described in Example 4, page 12 of the specification (i.e., vector, delivery method, dosage, type of injury; Decl. ¶2). This post-filing date data is relevant because the same procedures were used therein as were exemplified in the application. This data is not used to enable the invention; instead, it merely confirms that the specification was enabling as of its filing date. Thus, the

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skilled artisan would have received sufficient guidance from the specification as originally filed to practice the invention as claimed without undue experimentation (Decl., ¶3).

The PTO also stated that it was unlikely whether "a single intervention will be effective in limiting restenosis in humans (Ferrel, page 1631)." Because Applicants are no longer claiming inhibition of restenosis, this point is no longer at issue. The PTO further stated that "the evidence of long-term effectiveness for the invention in the porcine model..., as well as the accumulated results of animal studies using the invention, are not contained in the specification." Applicants are not obliged to demonstrate long-term effectiveness, as inhibition of restenosis is not being claimed. It has clearly been shown that expression of the tk gene leads to the desired results, namely inhibition of vascular cell proliferation.

Although Applicants do not exemplify the use of delivery systems other than adenovirus, the delivery of the genes using other viral and nonviral vectors is well known to those of ordinary skill in the art as stated in the declaration of Dr. Elizabeth Nabel submitted with Applicants' response filed February 10, 1995 (See ¶11) and as evidenced by the enclosed publication of Nabel et al. (*Science*, 1285-1288 (1990)). This publication describes in detail the use of retroviral and liposome-mediated gene delivery. The results detailed in the specification are not dependent on the particular mode of gene delivery; rather, those skilled in the art

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will appreciate that the tk gene, regardless of its mode of entry into the cell, expresses tk protein which phosphorylates ganciclovir, resulting in cell death and inhibition of vascular cell proliferation. Lipid mediated delivery is known to be effective for delivering DNA to cells.

The PTO also maintained that "delivery of vector at the time of mechanical injury might be insufficient to transduce enough cells to achieve the results of the exemplified adenoviral vector." This is clearly erroneous, as Applicants have demonstrated significant inhibition of vascular cell proliferation in three species using an adenoviral vector containing the hsv-tk gene. Thus, it is apparent that the method results in transduction of an adequate number of cells.

It is well settled that the Applicant is not required to test all the embodiments of his invention in order to meet the requirements of § 112. Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd. 18 U.S.P.Q.2d 1016, 1027 (Fed. Cir. 1991). In addition, Applicant need not test all the species within the scope of a generic claim. In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). Under § 112, first paragraph, the written description is sufficient for a broadly claimed invention even if it does not describe all species that a generic claim encompasses. Amgen, 18 U.S.P.Q.2d at 1027.

The PTO also asserted that because different mechanical injuries induced different patterns of vascular proliferation as

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shown by the Santoian reference, the skilled artisan would not reasonably expect that inhibition of restenosis would be observed for all types of mechanical injury. Although Applicants still disagree with this assertion, the claims have been amended to recite only balloon injury to expedite prosecution of the application.

To determine whether a specification is enabling, the factors to be considered are summarized in two leading decisions, Ex parte Forman, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. Int. 1986) and In re Wands, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988). These factors are the quantity of experimentation necessary, the amount of direction or guidance presented, the presence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims.

As discussed hereinabove, the specification as filed would enable the skilled artisan to practice the invention without undue experimentation as evidenced by subsequent successful experiments using the same materials and techniques detailed in the specification. Accordingly, the specification provides sufficient direction or guidance for the skilled artisan to practice the invention as claimed. *In vivo* working examples using an art-recognized porcine animal model are present in the specification, which evidence the operability of the claimed invention. The nature of the invention is straightforward, the inhibition of

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vascular cell proliferation using hsv tk in combination with a DNA replication-inhibiting nucleoside analog. The relative skill in the art of cardiovascular biology was high at the time the application was filed. Thus, the skilled artisan would clearly be able to practice the invention as claimed in view of the specification as filed.

Prior to the present invention, it was not predictable that vascular cell proliferation could be inhibited by transfecting blood vessel endothelium with the hsv tk gene followed by administration of a nucleoside analog which is modified by tk to produce a compound that killed proliferating cells. As stated in the declaration (Decl., ¶5), it was unexpected that such antiproliferative compounds would be effective due to the failure of previous compounds. Now, however, these uncertainties have been resolved using methods described in the instant application which were subsequently successfully employed *in vivo* using a variety of animal models.

The breadth of the claims is reasonable in view of the disclosure. The claims recite a method for inhibiting vascular cell proliferation associated with balloon injury of a blood vessel in a mammal by administering the tk gene to a blood vessel followed by administration of a DNA replication-inhibiting nucleoside analog thereto. They are commensurate in scope with the data in reciting the tk gene, balloon injury, and delivery via catheter instillation.

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As discussed herein, when one weighs these factors, the scales tip sharply in favor of enablement. The present invention clearly enables those of ordinary skill in the art to practice the claimed invention without undue experimentation.

In view of the arguments presented above, Applicants respectfully request withdrawal of the rejections under § 112.

Rejections under 35 U.S.C. § 103

The PTO maintained its rejection of the pending claims under § 103 as being unpatentable over Takeshita et al. in view of Plautz et al. According to the PTO, Takeshita et al. employs *in vivo* gene transfer for inhibition of restenosis. This statement is incorrect. Takeshita et al. only determine that PTA does not alter the transfection efficiency of a marker gene in atherosclerotic arteries *in vivo*.

Furthermore, Takeshita et al. only speculatively disclose "adjunctive gene transfer post-PTA as a potential strategy to reduce restenosis." The PTO has opined that the present invention was unpredictable at the time the application was filed. It has long been established that "obvious to try" is not the standard contemplated by § 103; there must also be a reasonable expectation of success at arriving at the claimed invention by combining the cited references. In re Goodwin, 576 F.2d, 377, 198 U.S.P.Q. 1, 3 (C.C.P.A. 1978).

Even if it were obvious to try the adenoviral HSV tk construct of Plautz et al. in the *in vivo* gene transfer method of Takeshita

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et al., the skilled artisan could not confidently predict that this vector would inhibit vascular cell proliferation due to the failure of others (Decl., ¶5) and the unpredictability of the field at the time the application was filed (Decl., ¶7). In addition, Plautz et al. transfected tumor cells with their suicide retroviral vector, while the instant method is directed to nontransformed blood vessels after mechanical injury. Because the mechanisms by which the two cell types proliferate is different, a treatment successful in inhibiting tumor cell (transformed cell) growth would not necessarily inhibit the growth of vascular smooth muscle cells (nontransformed cells) which have been subjected to mechanical injury. Indeed, Plautz et al. showed that blood vessels treated with hsv tk and ganciclovir were unaffected. If anything, this tends to teach away from treating nontransformed blood vessels using the claimed method.

As described in the Declaration, it was also unexpected that the instant method would effectively transduce enough vascular cells to manifest an effect due to the "washout" phenomenon (Decl., ¶7) and the expectation that the promotion of cell death would result in a pro-inflammatory response (Decl., ¶6), both of which unexpectedly did not occur. Further, the present invention fulfills a long felt but unsolved need (Decl., ¶4). Lastly, the invention has received critical acclaim by others in the field (Decl., ¶8). Thus, Applicants have shown that the invention demonstrates several indicia of nonobviousness which must always be

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considered by the PTO. Graham v. John Deere Co., 383 U.S. 1, 3-4, 86 S.Ct. 684, 686, 15 L.Ed.2d 545 (1966). This exceeds the standard of nonobviousness set by Graham v. John Deere.

The PTO rejected the remaining claims under § 103 based on various combinations of references, all relying on the combination of Takeshita et al. in view of Plautz et al. As discussed above, Takeshita et al. and Plautz et al. do not support an obviousness rejection. Thus, any combination of references relying on these two references also fails to render the claimed invention obvious.

In view of the arguments presented above, Applicants respectfully request withdrawal of all rejections under § 103.

Conclusion

Applicants submit that all claims are in condition for allowance and such allowance is earnestly solicited. However, if minor matters remain, the Examiner is invited to contact the undersigned at the telephone number provided below.

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Respectfully submitted,

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